Vincristine for Successful Treatment of Steroid-Dependent Infantile Hemangiomas

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abstract

Infantile hemangiomas (IHs) are common, although systemic therapy has been generally limited to circumstances of potential compromise of vital functions (airway, vision, feeding, or cardiac), risk of disfigurement, or bleeding. IHs have previously been shown to express high levels of type III deiodinase, which catabolizes active thyroid hormone, resulting in a state of severe hypothyroidism, termed “consumptive hypothyroidism.” We describe an infant with diffuse hepatic hemangiomas who developed consumptive hypothyroidism who was initially treated successfully with systemic glucocorticoids and β-blockers. Several efforts to wean her medications were unsuccessful. She subsequently developed severe growth restriction and treatment alternatives were sought. Although previously limited to treatment of life-threatening hemangiomas, a trial of vincristine was initiated. She was ultimately weaned from all systemic therapies, with recovery of a normal growth trajectory. This case highlights broader indications for vincristine as a safe and effective systemic therapy for treatment of IHs. It also stresses the importance of close anthropometric monitoring of infants and toddlers receiving glucocorticoid therapy and intervention when growth compromise becomes evident.

Infantile hemangiomas (IHs) are the most common benign vascular tumors in infancy and childhood. They occur in ~10% of births. They characteristically follow a triphasic growth pattern including proliferation, plateau, and involution. Spontaneous resolution is common, and thus treatment is generally limited to those circumstances in which airway, vision, cardiac function, or feeding are compromised or where there is risk of disfigurement or persistent bleeding. Consumptive hypothyroidism is a rare, albeit potentially morbid complication of IHs. It was initially described by Huang et al in association with a critically ill infant with hepatic hemangiomas. The infant required high doses of thyroid hormone replacement and ultimately succumbed to his illness. Overexpression of type III deiodinase within the hemangioma can result in a profound hypothyroid state. Type III deiodinase catalyzes the inactivation of thyroid hormones by converting biologically active T4 (thyroxine) and T3 (triiodothyronine) to inactive reverse T3 and T2 (diiodothyronine), respectively, via inner-ring deiodination. Subsequent reports of consumptive hypothyroidism have since been described in the setting of other hepatic and nonhepatic vascular tumors and, more recently, in gastrointestinal stromal tumors.

We describe an infant with steroid-dependent, diffuse hepatic hemangiomas and consumptive...
hypothyroidism who, in the course of systemic treatment, developed significant impairment of linear growth. The infant was treated with intravenous vincristine and was successfully weaned from all medications, achieving a clinically and biochemically euthyroid state, which highlights this therapeutic option as a viable ancillary option for systemic therapy of IHs.

PATIENT PRESENTATION

A 7-week-old girl presented for evaluation of progressive abdominal distension and jaundice. She was the healthy full-term product of an uncomplicated pregnancy. The family history was negative for endocrinopathies, early or atypical malignancies, hepatic disease, or infectious exposures. Prenatal serologies were normal, including negative hepatitis B and HIV titers.

Initial examination was notable for a well-appearing, nondysmorphic white infant with diffuse jaundice. There were no petechiae or ecchymoses. A single 1.5-mm hemangioma on the right palm was noted. She had a normal head and neck examination, no plethora, and a normal size tongue. There was no goiter. Her chest was clear to auscultation, and heart sounds were normal without gallop or murmur. The patient’s abdomen was markedly distended, with the hepatic edge palpable 14 cm below the right costal margin. The spleen was normal. There was no abdominal tenderness, and there were no caput medusae or spider angiomata.

Initial biochemical evaluation revealed cholestasis with normal transaminases. Thyrotropin was 123 mIU/L (0.5–5 mIU/L), free T4 was 9.3 pmol/L (10–23 pmol/L), total T3 was 0.8 nmol/L (1.6–4.4 nmol/L), and reverse T3 was 15.4 nmol/L (0.12–0.54 nmol/L). α-Fetoprotein was 1473 µg/L (40–1000 µg/L) and complete blood count was normal. Abdominal ultrasonography and computed tomography revealed diffuse hepatic hemangiomas and a solitary splenic lesion (Fig 1 A and B). There was normal flow through the hepatic vasculature and no obstruction of the biliary system. The provincial newborn screen was reviewed and confirmed to be normal, demonstrating a thyrotropin level of 3.5 mIU/L at 64 hours of life.

On the basis of her significant hypothyroidism and sonographic evidence consistent with multiple hepatic hemangiomas, a presumptive diagnosis of consumptive hypothyroidism secondary to overproduction of type III deiodinase was established.

FIGURE 1

Arterial-phase, contrast-enhanced abdominal computed tomography reveals numerous hypervascular lesions within both lobes of the liver in axial section (A) and coronal reconstruction (B). These lesions show nodular peripheral enhancement on the arterial phase and partial filling in by contrast during the portal venous phase (not shown). The appearance is typical of infantile hepatic hemangiendotheliomatosis. The superior pole of the kidneys is identified with arrows (A). C, Serum biochemical results during the course of therapy. Reference ranges for all analytes (as specified in the text) are shaded in gray. D, Dosages of exogenous thyroid hormone corresponding to thyroid function tests in (C). E, Hemangioma-targeted therapy dosages during treatment. TSH, thyroid-stimulating hormone (thyrotropin); T3, triiodothyronine; T4, thyroxine.
CLINICAL COURSE

Thyroid replacement was initiated with liothyronine (T3) 1.3 μg/kg per day divided twice daily and prednisone 2 mg/kg per day (hydrocortisone equivalent: 200 mg/m² per day). An initial increase in thyrotopin to 244 mIU/L 3 weeks after initiation of therapy prompted the addition of levothyroxine (T4) at 8.9 μg/kg per day and propranolol at 2 mg/kg per day. Within 3 weeks, thyrotopin declined to near-normal levels (thyrotopin = 6.14) and a steroid taper was commenced. Repeat ultrasound revealed a slight decrease in the size of the hemangiomas. One month after discontinuation of steroid therapy, thyrotopin had rebounded to 71.2 mIU/L, prednisone was resumed, and propranolol increased (Fig 1E). Thyroid replacement was adjusted biweekly to target thyrotopin levels within the reference interval. Levothyroxine replacement reached a maximum dose of 21 μg/kg per day and liothyronine reached a maximum of 4 μg/kg per day. The initial liver function abnormalities and elevated α-fetoprotein resolved within 3 months of treatment and remained normal thereafter. Two subsequent attempts to wean glucocorticoids were unsuccessful and the child remained steroid-dependent for the subsequent 12 months.

At 14 months, significant growth restriction was noted, with length and weight well below the first percentile for age, despite adequate nutrition (Fig 2). Persistent steroid requirement, high doses of thyroid replacement, and concerns for iatrogenic growth retardation prompted consideration of alternate therapies. The multiple lesions were not amenable to embolization. Although liver transplantation was reported to reverse consumptive hypothyroidism in 2 patients with hepatic hemangiomas,4,8 given the patient’s otherwise excellent functional status and available medical options we elected to pursue nonoperative therapy. Weekly vincristine infusion was initiated at 14 months at a dose of 0.03 mg/kg per dose. After 7 doses without biochemical or radiographic response, the dose was escalated to 0.05 mg/kg per dose and continued weekly at this dose for an additional 20 weeks. The child was monitored routinely for adverse effects of vincristine and experienced none. Specifically, there was no peripheral neuropathy, constipation, or cytopenia.

During the course of vincristine therapy, prednisone was successfully weaned completely, whereas a normal thyrotopin was maintained. The child was gradually weaned from all medications by 5.2 years and remains clinically and biochemically euthyroid after an additional year of follow-up. There was minimal sonographic decrease in the tumor burden at 5 years of age; however, by age 6 the radiographic appearance was consistent with generalized involution as the lesions became more sonographically indistinct from hepatic parenchyma. Growth retardation resolved after the withdrawal of glucocorticoids and the child has assumed her genetically predicted growth trajectory.

FIGURE 2

Recumbent length (0–2 years) and standing height (2–5 years) during therapy for consumptive hypothyroidism according to World Health Organization length/height-for-age growth standards for girls from birth to age 5 years.23 Relative dosages of hemangioma-targeted therapies are indicated.
Throughout the course of treatment, the patient remained clinically euthyroid. Developmental milestones were met age-appropriately. The patient remains in active follow-up with serial biochemical evaluation and imaging.

**DISCUSSION**

Therapy for IHs is indicated only in cases in which there is potential compromise of vital functions, disfigurement, or bleeding. Glucocorticoids have traditionally been the mainstay of systemic therapy, but are not without consequences, including secondary adrenal insufficiency, impairment of bone accretion, and growth compromise. Approximately 16% of hemangiomas do not respond to steroid therapy. β-Blockers were serendipitously identified to promote regression of IHs and have assumed an increasingly prominent role in their treatment. β-Blockers are now considered standard-of-care first-line systemic therapy. Vincristine has been described for treatment of life-threatening and/or corticosteroid-resistant hemangiomas, however, its use in treating IHs for other indications is limited. In this report, we expand the indications for vincristine use to include hemangiomas in patients with treatment-related morbidity.

The evolution of disease in this child is consistent with the natural history of IHs, which typically proliferate after birth and subsequently undergo spontaneous involution by 8 to 9 years of age. The tumor burden in this child and the associated hormonal abnormalities prompted early aggressive treatment to attempt to promote more rapid tumor involution.

This case identifies the challenging management of a child with hepatic hemangiomas resulting in consumptive hypothyroidism. Although responsive to glucocorticoids as a component of multiagent therapy, growth-suppressive consequences necessitated exploration of alternate treatments.

Several therapeutic challenges characterized this child’s care. Initial attempts to reestablish biochemical euthyroidism required multidrug therapy targeted at both thyroid hormone supplementation and at stabilization of the tumor; with eventual efforts to accelerate involution. Medical stabilization was ultimately achieved with a 4-drug regimen; however, iatrogenic complications limited the continuation of this approach and prompted consideration of alternate strategies.

Vincristine is an antiangiogenic agent that acts via inhibition of cell mitosis and microtubule formation. It has been reported to be effective in life-threatening IHs and other vascular anomalies including tufted angiomas and kaposiform hemangioendotheliomas. The introduction of vincristine in this circumstance allowed withdrawal of glucocorticoids within a period of weeks and was followed by tapering of all medications. Although it is possible that this response represented, in part, the physiologic involution of the tumors, there had been little radiographic interval change, despite biochemical resolution. This observation highlights that biochemical activity is separable from radiographic appearance with respect to treatment response.

Other systemic therapies for second-line therapy of IHs have been proposed, including interferon α and sirolimus. Interferon therapy is complicated by treatment-related toxicities including fever, irritability, malaise, liver function abnormalities, and neutropenia, although the potential for irreversible neurotoxicity (including several reports of spastic diplegia) substantially limits its consideration as second-line therapy. It remains to be demonstrated which of these therapies is most appropriate; however, this report suggests vincristine to be a viable option that carries a tolerable side-effect profile. We suggest vincristine to be an effective and safe adjunct therapy for systemic treatment of complicated IHs and that indications for use may expand beyond life-threatening situations to include those circumstances with first-line treatment failure and/or treatment-associated morbidity, provided appropriate clinical and biochemical monitoring is instituted.

**REFERENCES**


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